15) The process of claim 4 wherein delivering the nucleic acid includes increasing internal pressure of the heart vessel.

16) The process of claim 15 wherein delivering the nucleic acid includes increasing the heart vessel permeability.

18) A process for gene expression providing a therapeutic protein, comprising:

a) inserting a nucleic acid into a blood vessel having a channel leading to heart muscle;

b) delivering the nucleic acid to a heart muscle cell; and,

c) expressing the nucleic acid to provide a therapeutic protein.

REMARKS

Objection to the Specification under 35 U.S.C. 112:

Claims 18-20 have been rejected under §112. On pages 3-4, the Office Action states that the specification does not provide a way to make and/or use the invention. Applicants respectfully disagree with the rejection.

The levels achieved indicate a reasonable expectation of any gene expression to a person having skill in the art of methods of delivery. The examiner agrees "in part that the delivery of a nucleic acid is not limited structurally" (page 3). It is well accepted in the field of gene therapy that delivery and expression of a reporter gene is predictive of delivery of therapeutic genes. There are no inherent reasons that a therapeutic protein cannot be expressed in amounts similar to the reporter gene. It is known to those skilled in the art that an appropriate therapeutic gene (and expression cassette) should be chosen to obtain a desired therapeutic effect. For any particular disease state where gene therapy may be applied, it is necessary to determine the effectiveness of a chosen therapeutic gene. Experiments may be carried out in appropriate animal models and in human clinical trials.

The Office Action states that successful implementation of gene therapy protocols was not routinely obtained by those skilled in the art. However, recent successes have been recognized: Somia and Verma reviewed therapeutic results regarding "the successful treatment of three children suffering from a rare but fatal immunological disease."

With this Response, Applicants submit a §132 Declaration containing an example of *in vivo* gene therapy. Applicants' process was used to inject pigs with vascular endothelial growth factor (VEGF) which yielded therapeutic levels of expression.

Therefore, Applicants believe they have reasonably described and enabled their invention. Applicants respectfully request that the §112 be removed.

Objection to the Specification under 35 U.S.C. 112:

Claims 1-20 have been rejected under §112 second paragraph for being indefinite.

On page 4 of the Action, the claim is objected to for being unclear as to targeting the heart. Applicants are not targeting the heart *per se*. The heart muscle cell will express nucleic acids associated with a promoter that it recognizes. Applicants are not concerned with nucleic acid that is delivered to other tissue cells by their process since they are unlikely to express a nucleic acid that is not associated with the cell type. In the unlikely instance where a non-heart cell expresses a delivered nucleic acid erroneously, expression will be ineffective.

On page 5, claim 1 is rejected for the use of "heart tissue cell." The claim has been amended to substitute "heart muscle cells" to obviate the rejection. Support for the amendment may be found in the specification on page 8, line 38 and throughout.

On page 5, claims 6, 11, 14 and 17 are objected to for being vague, unclear and indefinite because it is not clear if the nucleic acid contained in the virus is the viral genome or other nucleic acids. These claims have previously been amended to include the modifier "nucleic acid contained in viruses" as suggested in the first Office Action. The term "nucleic acid contained in viruses" refers to the (natural or recombinant) viral genome. Support for the definition may be found in the specification on page 15, line 6. The combination of "an artificially created capsid containing a plasmid" would be considered a complex between a nucleic acid (plasmid DNA) and a transfection reagent (the artificially created capsid). Support for the definition may be found in the specification on page 13, line 1. In this example, the nucleic acid would be a plasmid DNA and not a nucleic acid contained in a virus.

Claim 7 is objected to on page 5. Claim 7 has been canceled therefore the objection is obviated.

Claim 18 is objected to for containing no process steps where therapy occurs. Claim 18 has been amended to remove the term "gene therapy" and insert "gene expression providing a therapeutic protein." Applicants believe the objection is obviated.

Rejection of claims under 35 U.S.C. 102:

Claims 1-17 are rejected under §102(a) as being anticipated by Mann *et al.*, Isner *et al.* and Hajjar *et al.* Applicants have amended the claims to remove the rejection.

Applicants have amended claim 1 to include the language: "there is not more than one heart vessel occlusion site per introduction." All of the prior art references cited require occlusion of the vessel in the form of a double balloon catheter. The double balloons occlude the vessel proximal to the injection site and distal from the injection site. A double occlusion prevents blood flow at two sites and may induce injury to the blood vessel as well as other possible complications. Conversely, Applicants can perform their method without restricting the vessel by a double occlusion providing a simplified and a less invasive process. Additionally, their delivery

area is not restricted to the area between the two balloons. Support for this amendment may be found in the Specification on page 9, lines 7-8 and the examples.

With this Amendment and Response, Applicants have provided a Declaration under 37 CFR 1.131 wherein an inventor swears behind the Hajjar *et al.* reference which published in April, 1998. The inventor also has notebook pages that show conception more than one year prior to the Hajjar *et al.* publication if requested by the Examiner.

Rejection of claims under 35 U.S.C. 103:

Claims 1-20 are rejected under §103(a) as being obvious over Mann *et al.* in view of Morishita *et al.* Applicants respectfully disagree.

As stated in Applicants' response above, Mann *et al.* did not disclose nucleic acid transfer via a vessel without the use of a double restriction on vessel flow at and away from the injection site. The Mann *et al.* procedure is very invasive by their use of an external enclosure or description of a double balloon catheter. It would not be obvious from the Mann reference to consider injecting a nucleic acid without downstream vessel occlusion.

Supplemental Material:

Applicants have provided additional material with this Amendment and Response in the form of a 37 CFR 1.132 Declaration. The material consists of experiments performed using Applicants' processes providing a therapeutic result. The experiments show *in vivo* injection of nucleic acids, which express vascular endothelial growth factor (VEGF), into pigs. The material is submitted to support Applicants' assertions of probable therapeutic protein expression by showing actual therapeutic protein expression.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendments and discussion, it is submitted that claims 1-6 and 12-22 should be allowable and Applicants respectfully request an early notice to such effect.

Respectfully submitted,

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